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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/763,362 | 04/23/2001 | Kazuma Tomizuka | 081356/0158 | 4670 |
| 7590 Foley & Lardner Washington Harbour Suite 500 3000 K Street NW Washington, DC 20007-5109 | | | EXAMINER TON, THAIAN N | |
| | | | ART UNIT 1632 | PAPER NUMBER |
| SHORTENED STATUTORY PERIOD OF RESPONSE 3 MONTHS | | MAIL DATE 04/23/2007 | DELIVERY MODE PAPER | |

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

| | | | |
|------------------------------|-----------------|-----------------|--|
| Office Action Summary | Application No. | Applicant(s) | |
| | 09/763,362 | TOMIZUKA ET AL. | |
| | Examiner | Art Unit | |
| | Thaian N. Ton | 1632 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 04 February 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 26-83, 85, 93, 96-112, 117-124, 126, 135, 136 and 138 is/are pending in the application.
- 4a) Of the above claim(s) 26-83 and 85 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 93, 96-112, 117-124, 126, 135, 136 and 138 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/4/07 has been entered.

Applicants' Amendment and Remarks, filed 2/7/07, have been entered. Claims 26-83, 85, 93, 96-112, 117-124, 126, 135, 136 and 138 are pending; claims 26-83 and 85 are withdrawn; claims 93, 96-112, 117-124, 126, 135, 136 and 138 are under current examination.

Election/Restrictions

Claims 26-83 and 85 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected groups, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 8/9/02.

Response to Arguments

Applicants' Amendment to the claims overcomes the prior rejection of record, with regard to claims 93, 96-112, 117-124, 126, 135, 136 and 138, under 112, 1st paragraph for the enablement requirement. In particular, Applicants' have now amended the claims to no longer recite the term "entire antibody gene locus". As such, the prior rejection of record is withdrawn.

New rejections appear below.

Claim Objections

Claim 100 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 99. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). In particular, both claims have the identical scope, namely that the chromosome #14 fragment comprises the human antibody heavy chain gene, and the chromosome #2 fragment comprises the human antibody light chain kappa gene.

Similarly, claim 103 is a substantial duplicate of claim 102, because both claims have the identical scope, namely that the human heavy chain gene is from chromosome #14 and the human antibody light-chain lambda gene is from chromosome #22.

Claim 105 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The claim recites that the human chromosome comprises the human antibody heavy chain gene. However, this limitation is already recited in part (iv) of claim 93 (the independent claim from which claim 105 depends).

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 135 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claim does not sufficiently distinguish

between cells that would occur *in vivo* and *in vitro*. Thus, this claim encompasses any non-isolated cell (including of human origin) that comprises the human recombinant chromosome. The claims should be amended to indicate the hand of the inventor, e.g., by insertion of "Isolated" or "Purified".

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 93, 96-112, 117-124, 126, 135, 136 and 138 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

1. An isolated recombinant human chromosome comprising
 - i) the SC20 chromosome fragment (Accession No. FERM-BP-7583) which comprises the human chromosome #14 centromere,
 - ii) two telomere sequences;
 - iii) at least one recognition sequence for a site directed recombination enzyme;
 - iv) at least two fragments from different human chromosomes, wherein each fragment comprises an antibody gene, wherein one of the fragments comprises a human chromosome #14 fragment which comprises the human antibody heavy-chain gene, and wherein a second chromosome fragment comprises either a human chromosome #2 fragment which comprises the human antibody light chain kappa gene, or a human chromosome #22 fragment which comprises the human antibody light chain lambda gene;
 - (v) a marker gene,

wherein the recognition sequence for the site directed recombination enzyme is located between the chromosome fragments.

2. An isolated cell comprising said human recombinant chromosome
3. A method for producing a recombinant human chromosome comprising:
 - a) preparing a first isolated cell comprising the SC20 chromosome fragment (Accession No. FERM-BP-7583), which comprises the human #14 centromere;
 - b) preparing a second, isolated cell comprising a human chromosome fragment which comprises i) a human antibody gene and ii) a recognition sequence for a site-directed recombination enzyme at a desired site in the chromosome fragment;
 - c) fusing said first cell with said second cell to produce a hybrid cell; and
 - d) expressing a site directed recombination enzyme in said hybrid cell;

wherein expression of said enzyme causes site-directed recombination between the SC20 chromosome fragment comprising the human #14 centromere, and a portion of the second chromosome fragment;

thereby producing a human recombinant chromosome.

The specification does not reasonably provide enablement for the breadth of the claims, which encompasses the human antibody heavy chain gene that is located on human chromosomes other than human chromosome #14, the human antibody light chain kappa gene, located on human chromosomes other than human chromosome #2, and the human antibody light chain kappa gene, located on any other human chromosomes, other than the human chromosome #22; using cells that comprise chromosomes fragments that comprise a human antibody gene, other than

human chromosome fragments to produce the recombinant human chromosome; non-isolated cells comprising the human recombinant chromosome. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

The claimed invention is directed to a recombinant human chromosome comprising SC20 (Accession No. FERM BP-7583), a chromosome fragment that contains the human chromosome #14 centromere, two telomere sequences, at least one recognition sequence for a site-directed recombination enzyme and at least two fragments from different human chromosomes, wherein each fragment comprises an antibody gene, wherein one of the fragments comprises a human antibody heavy-chain gene, and wherein chromosome fragment comprises a human antibody light chain kappa gene, or a human antibody light chain lambda gene; and a marker gene, wherein the recognition sequence for the site directed recombination enzyme is located between the chromosome fragments.

The breadth of the claims encompasses human antibody heavy-chain genes that are located on human chromosomes other than human chromosome #14, the human antibody light chain kappa gene, located on human chromosomes other than human chromosome #2, and the human antibody light chain kappa gene, located on any other human chromosomes, other than the human chromosome #22. This is not enabling, because the art teaches that the human antibody heavy chain, light chain kappa gene, and light chain lambda gene are located on human chromosomes 14, 2

and 22, respectively. The breadth of the claims encompasses other chromosomal locations for these genes. For example, Matsuda *et al.* (J. of Exp. Med., 188(11): 2151-2162, December 7, 1998) state that, "The Ig molecule is encoded by three independent gene loci, namely Igk and Igλ for the L chain and IgH genes for the H chain, which are located on chromosome 2, chromosome 22, and chromosome 14 respectively." See p. 2151, 2nd col., 1st ¶. Thus, the Examiner has determined the scope of enablement, for part (iv) of claim 93, for example, to be limited to a human chromosome #14 fragment which comprises *the* human antibody heavy-chain gene, and wherein a second chromosome fragment comprises either a human chromosome #2 fragment which comprises *the* human antibody light chain kappa gene, or a human chromosome #22 fragment which comprises *the* human antibody light chain lambda gene. Note that the Examiner uses the term "the" to describe each gene, because, as taught by Matsuda, there is only one such gene (heavy chain, light chain kappa or light chain lambda) that is found in the human genome.

Finally, with regard to the method claims, these claims are only enabled for utilizing the SC20 chromosome fragment. As written, the method steps state that the fragment of human chromosome #14 is obtained from the SC20 fragment. As noted in prior Office actions, it is the SC20 fragment, itself, that is used, and has been determined to be within the enabled scope. See also, Figure 58, which shows the production of the human recombinant chromosomes of the instant invention.

Accordingly, in view of the state of the art, with regard to the chromosome locations of the human antibody heavy, light chain kappa, light chain gamma genes; the breadth of the claims, which encompasses these genes on different chromosomes, the lack of teaching or guidance provided by the specification with regard to using a fragment, other than the SC20 chromosome fragment, it would have required undue experimentation, for one of skill in the art, to make and use the claimed invention.

Written Description

Claims 122 and 138 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that, “[A]pplicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the ‘written description’ inquiry, *whatever is now claimed*.” *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d at 1117. The specification does not, “clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.” *Vas-cath Inc. v. Mahurkar*, 19USPQ2d at 1116.

The claims are directed to metdhos of producing a human recombinant protein, wherein the site-directed recombination is detected by the expression of a reporter gene, which is green fluorescent protein (GFP) or a functional variant thereof. The specification provides sufficient written description for using GFP as a reporter gene, but the term functional variant thereof lacks a written description. The claimed invention *as a whole* is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which are not conventional in the art as of Applicants effective filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998).

In the instant case, *a functional variant thereof* is not described by the instant specification. For example, a functional variant of a reporter gene need not have a structural similarity to the reporter gene. Thus, this term could encompass genes that are structurally related to GFP (such as YFP, RFP), or other, unrelated genes that are used as reporter genes (such as luciferase). The specification fails to describe the functional variants of reporter genes that fall within this genus, and the skilled artisan cannot envision which, when use as claimed, would result in the production of a human recombinant chromosome. Therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGFs were found to be unpatentable due to lack of written description for that broad class. The specification only provided the bovine sequence.

Applicant is reminded that *Vas-Cath* makes clear that the written description of 35 U.S.C. 112 is severable from its enablement provision [see p. 1115].

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 96-98, 100, 104, 105 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 96-98, as written are unclear, because the claims recite that one of the fragments is a human #2, #22, or #14 fragment. However, Matsuda *et al.* (cited above) clearly show that chromosome #2 can only contain the human light chain kappa gene; chromosome #14 can only contain the human antibody heavy-chain gene, chromosome #22 can only contain the human antibody light chain lambda gene. Thus, the metes and bounds are unclear, unless the corresponding chromosome is recited with the appropriate gene that is found on that chromosome. Claim 100 depends from claim 98.

Claim 104 recites the limitation "the chromosome fragment denoted as SC20" in the last line of the claim. There is insufficient antecedent basis for this limitation in the claim. It is suggested that the claim be written to recite "the SC20 chromosome fragment". Claim 105 depends from claim 104.

Art Unit: 1632

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Thursday from 7:00 to 5:00 (Eastern Standard Time). Should the Examiner be unavailable, inquiries should be directed to Peter Paras, SPE of Art Unit 1632, at (571) 272-4517. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the Official Fax at (571) 273-8300. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Thaian N. Ton
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